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# Automatic Generation of Functional Annotation Rules Using Inferred GO-Domain Associations

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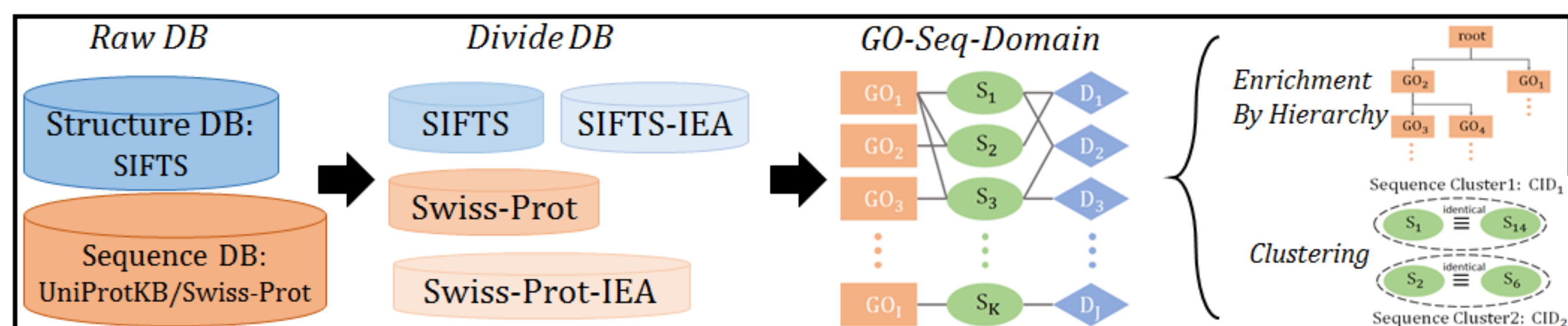
## Introduction

The GO ontology is widely used for functional annotation of genes and proteins. It describes biological processes (BP), molecular function (MF), and cellular components (CC) in three distinct hierarchical controlled vocabularies. At the molecular level, functions are often performed by highly conserved parts of proteins, identified by sequence or structure alignments and classified into domains or families (SCOP, CATH, PFAM, TIGRFAMs, etc.). The InterPro database provides a valuable integrated classification of protein sequences and domains which is linked to nearly all existing other classifications. Interestingly, several InterPro families have been manually annotated with GO terms using expert knowledge and the

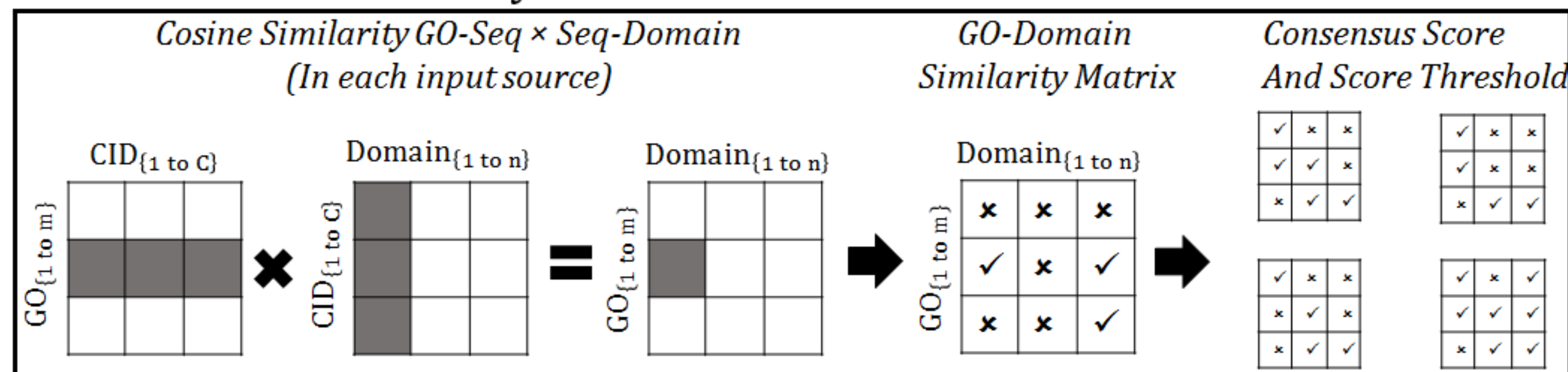
literature. However, the list of such annotations is incomplete (only 20% of Pfam domains and families possess MF GO functional annotation). We therefore developed the GODomainMiner approach to expand the available functional annotations of protein domains and families (1). Based on our ECDomainMiner approach (2), we use the respective associations of protein sequences with GO terms and protein domains to infer direct associations between GO terms and protein domains. Finally, we used our calculated GO-Domain associations to devise a systematic way, called AutoProf-Annotator, to generate high confidence rules for protein sequence (or structure) annotation.

## Prediction flowchart

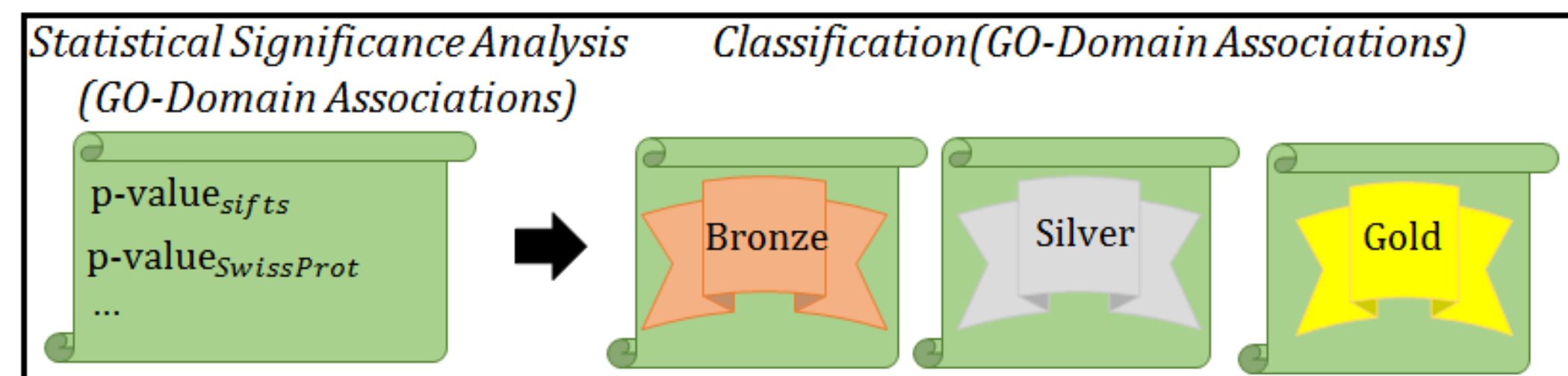
### Input



### GO-Domain Similarity Matrix

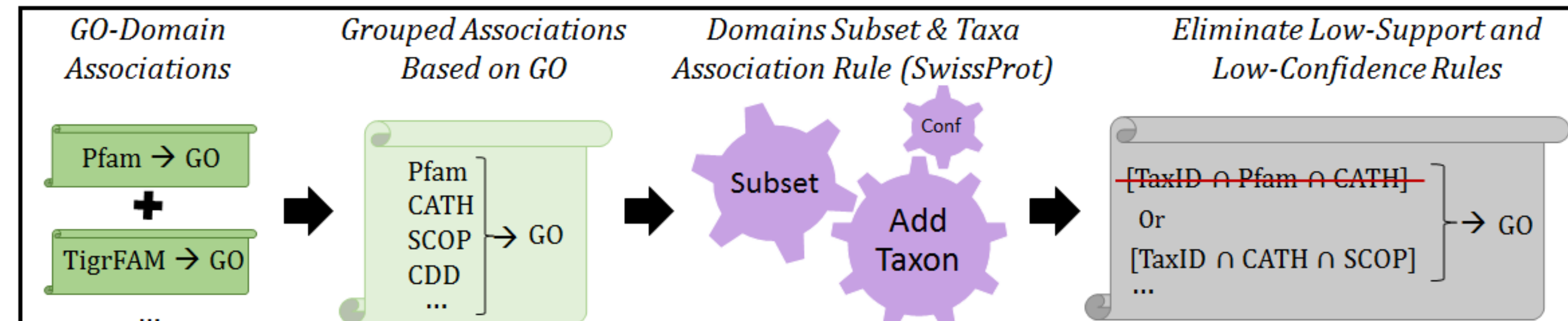


### P-Value and Classification

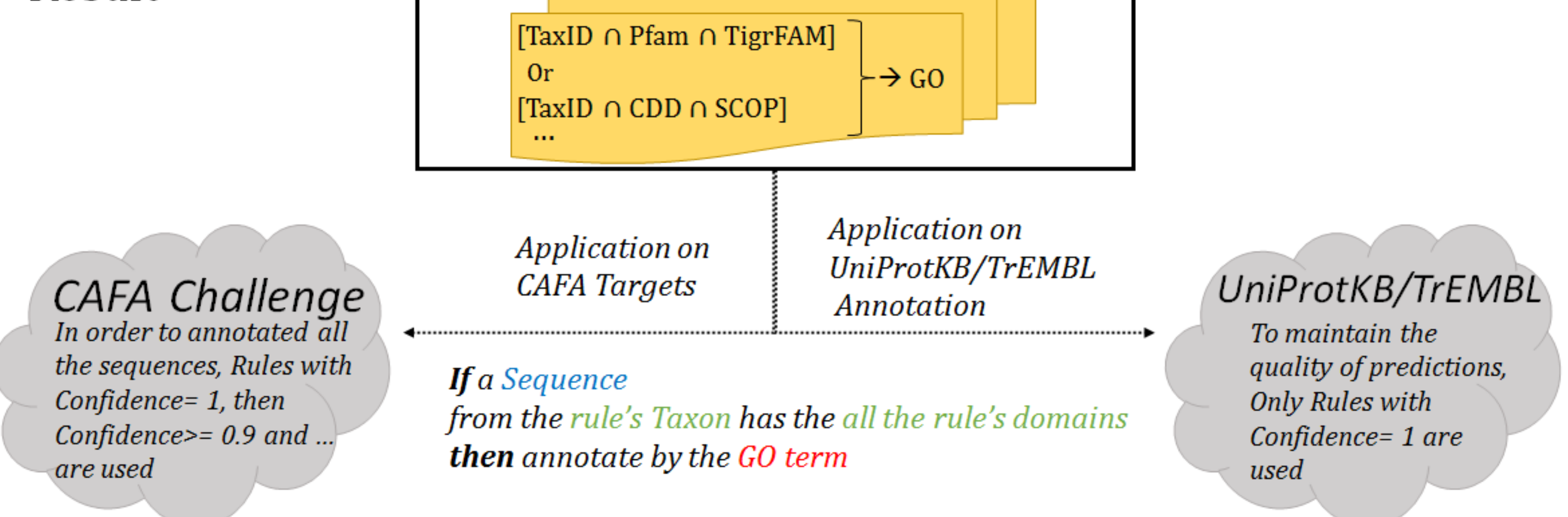


### GODomainMiner

### Association Rule Generation



### Annotation Rules Result



### AutoProf-Annotator

## Rules Statistics

AR Confidence > 0.5	Molecular Function	Biological Process	Cellular Component
Combination of Domains	1,723,497	1,841,000	1,543,333
Distinct Taxon	8,337	8,237	8,276
Prediction Rules	4,705	11,676	1,870

Table 1. Numbers of rules and the combination of domains result in the all rules.

AR Confidence = 1	Molecular Function	Biological Process	Cellular Component
Combination of Domains	1,692,547	1,826,347	1,496,772
Distinct Taxon	8,332	7966	8,266
Prediction Rules	4,673	11,582	1,853

## Association Rule Samples

### Rule (Confidence = 1)

- $\{ \{ \{ PF02423 \cap CATH:3.30.1780.10 \} \cap Mammalia \} \rightarrow GO:0047127 \}$
- PF02423: Ornithine cyclodeaminase/mu-crystallin family.
- CATH: 3.30.1780.10: Ornithine cyclodeaminase.
- MF GO:0047127: hiomorpholine-carboxylate dehydrogenase.

### UniProtKB/Swiss-Prot:

- Hits: 5 sequences, all are annotated with the GO term.

### UniProtKB/TrEMBL Annotation

- Hits: 47 Sequences.
- 1 Sequence is annotated with the GO term.
- 7 Sequence are annotated with ancestors of the GO term (General)
- 39 Sequence are annotated by AutoProf-Annotator

### Rule (Confidence = 1)

- $\{ \{ \{ CD01399 \} \cap Proteobacteria \} \rightarrow GO:0046348 \}$
- CD01399: GlcN6P\_deaminase.
- BP GO:0046348: amino sugar catabolic process.

### UniProtKB/Swiss-Prot:

- Hits: 103 sequences, all are annotated with the GO term.

### UniProtKB/TrEMBL Annotation

- Hits: 1930 Sequences.
- 1171 Sequence is annotated with the GO term.
- 569 Sequence are annotated with ancestors of the GO term (General)
- 190 Sequence are annotated by AutoProf-Annotator

## Summary of CAFA Challenge Predictions

### Molecular Function GO

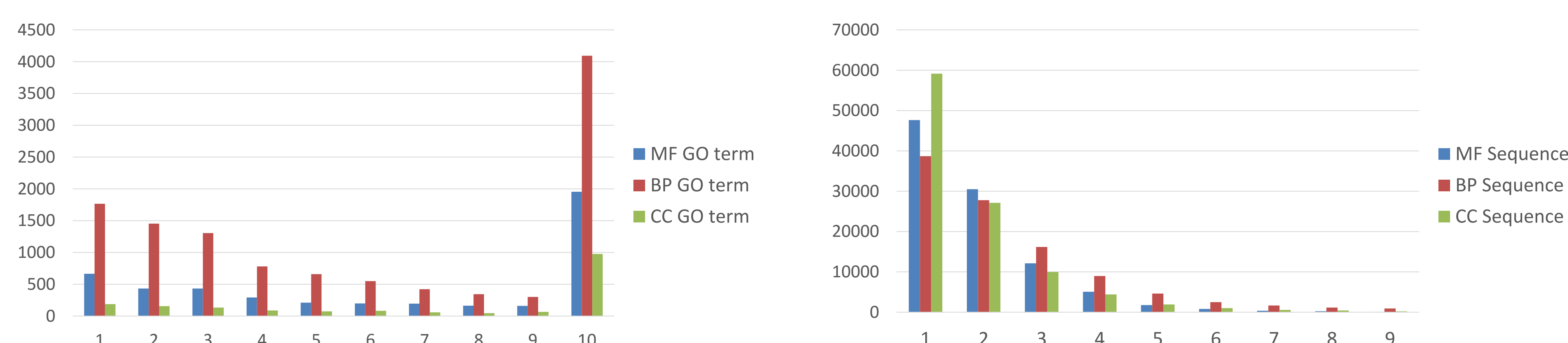
### Biological Process GO

### Cellular Component GO

Table 2. GO function prediction for 130,000 CAFA Targets.

	CAFA Targets	CAFA Targets (Conf. 1)		CAFA Targets	CAFA Targets (Conf. 1)		CAFA Targets	CAFA Targets (Conf. 1)
Prediction	188,549	164,359	Prediction	315,310	229,006	Prediction	191,835	150,411
Sequence	98,849	81,248	Sequence	106,346	72,543	Sequence	105,274	76,233
GO term	4,705	4,673	GO term	11,676	11,582	GO term	1,870	1,853
Common to existing GO terms	ISMB/ECCB Function SIG	ISMB/ECCB Function SIG	Common to existing GO terms	ISMB/ECCB Function SIG	ISMB/ECCB Function SIG	Common to existing GO terms	ISMB/ECCB Function SIG	ISMB/ECCB Function SIG

Fig2. CAFA3: Distribution according to the number of GO terms for each sequence (right), and sequences for each GO term (left)



## Annotation Examples

### PRS56\_Human is a target of CAFA3

- Very well annotated protein sequence in UniProtKB/Swiss-Prot
- Annotation Score: 5 - Experimental evidence at protein level
- Existing information in UniProtKB/Swiss-Prot:
  - MF **GO:0004252**
  - BP **GO:0043010**
  - BP **GO:0006508**
  - CC **GO:0005783**
- AutoProf-Annotator predicts following GO terms:
  - MF **GO:0004252** (Exact Match) (Conf. = 1)
  - BP **GO:0044699** (Ancestor of **GO:0043010**) (Conf. = 0.6)
  - BP **GO:0019538** (Parent of **GO:0006508**) (Conf. = 0.7)
  - CC **GO:0044464** (Ancestor of **GO:0005783**) (Conf. = 0.7)

### 6PGL\_SALCH is a target of CAFA3

- Annotated protein sequence in UniProtKB/Swiss-Prot
- Annotation Score: 2 - Protein inferred from homology
- Existing information in UniProtKB/Swiss-Prot:
  - MF **GO:0017057**
  - BP **GO:0006006**
  - BP **GO:0006508**
- AutoProf-Annotator predicts following GO terms:
  - MF **GO:0017057** (Exact Match) (Conf. = 1)
  - BP **GO:0006006** (Exact Match) (Conf. = 1)
  - BP **GO:0006508** (Exact Match) (Conf. = 1)
  - CC **GO:0042597** (New Prediction) (Conf. = 0.9)

## CONCLUSION

Our GODomainMiner approach provides a substantial enrichment of functional annotations at the protein domain level which has been exploited to develop a novel system here called AutoProf-Annotator for protein functional annotation. We used the AutoProf-Annotator to annotate target sequences in CAFA challenge.

## LITERATURE CITED

1. Alborzi, Seyed Ziaeddin, Marie-Dominique Devignes, and David W. Ritchie. "Associating Gene Ontology Terms with Pfam Protein Domains." International Conference on Bioinformatics and Biomedical Engineering. Springer, Cham, 2017.
2. Alborzi, Seyed Ziaeddin, Marie-Dominique Devignes, and David W. Ritchie. "ECDomainMiner: discovering hidden associations between enzyme commission numbers and Pfam domains." BMC bioinformatics 18.1 (2017): 107.

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